Psychosocial and Immunological Factors in Neurasthenia

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Background: *Neurasthenia is a disorder whose pathogenesis is still unknown.* **Objective:** *The authors sought to examine the relationships between neurasthenia and possible psychosocial and immunological correlates.* **Method:** *A sample of 30 Chinese neurasthenic patients was compared with a matched sample of 30 control subjects for 1) the level of serum Epstein-Barr virus (EBV) gamma G immunoglobulin (IgG) and gamma M immunoglobulin (IgM); 2) scores on the Eysenck Personality Questionnaire (EPQ); 3) the Symptom Checklist–90; and 4) the Life Event Scale (LES); 27 of the 30 neurasthenia patients were treated with medication and psychotherapy for a 4-month period, with measures taken pre- and posttreatment.* **Results:** *As compared with the control group, neurasthenic patients exhibited higher EPQ scores for neuroticism, higher levels of introversion, and a higher number of negative life events. Within the neurasthenia sample, scores for neuroticism and the SCL–90 Global Severity Index were significantly lower at follow-up than at baseline.* **Conclusion:** *As compared with control subjects, neurasthenia patients were characterized by greater neuroticism and introversion, and they reported a higher rate of negative life events. Moreover, the positive rate of EBV in neurasthenic patients was higher, which may be associated with higher EBV activation under states of stress.* (Psychosomatics 2009; 50:24–29)

Neurasthenia is a disorder whose pathogenesis is still unknown. It is characterized by prolonged and/or disabling fatigue resulting in significant functional impairment.[1–3] Various studies have shown that unexplained fatigue is a common condition in both community[4,5] and primary-care settings.[6,7] In the United States, an estimated 24% of the general adult population report fatigue lasting 2 weeks or longer; with 59% to 64% of these fatigue cases unexplained by medical causes.[8] This kind of unexplained fatigue has been classified and defined as "chronic fatigue syndrome" (CFS) by the Centers for Disease Control (CDC).[9] In China and other East Asian countries, neurasthenia is more likely to be diagnosed, suggesting a conceptual, if not biological, overlap in the two entities. For example, a transcultural study has shown that CFS and neurasthenia have similar symptom presentations and that medically and psychiatrically unexplained fatigue is the core feature of both illnesses.[2] For example, Hickie et al.[10] found 13.29% of an Australian community sample reporting prolonged or excessive fatigue, with nearly 10% of these patients actually fulfilling criteria for neurasthenia and sharing many of the symptoms of CFS. Wessely[11] concluded that the diagnosis of neurasthenia in the West has declined in light of current interest in CFS and suggested that whether or not it is worthwhile to distinguish between "neurasthenia" and CFS must depend on further clarification of the distinction between these syndromes.

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In the pathogenesis of CFS, psychosocial aspects, as well as immunological abnormalities, have been reported in the literature.[12–16] The Epstein-Barr virus (EBV) has been proposed as one possible pathogenic agent in CFS. On one hand, EBV-infected individuals may suffer from prolonged and chronic fatigue. On the other hand, CFS patients have high antibody titers to viral capsid antigen (VCA) and early antigen (EA) of EBV, suggesting that reactivation of EBV may be involved in patients with CFS. Thus, serum antibody to EBV VCA IgM may be a potential biochemical marker.[15,17] Similar data were reported in Japan.[18]

EBV is one type of human herpes virus. EBV infections are common in human beings; they are often mild, and may pass undiagnosed. Typically, EBV remains latent in a small proportion of B lymphocytes when immunity is secure, and it can be reactivated under immunosuppressed states.[19] The activity model of "latency–reactivity" with the positive EBV antibodies is associated with the relapsing–remitting pattern associated with CFS.[20]

Because of the substantial symptom and conceptual overlap between neurasthenia and CFS, it is possible that the immunologic and psychosocial correlates of CFS extend to the clinical syndrome of neurasthenia, as well.[2,3,20] Along these lines, we hypothesize that there is a correlation between personality, life stress, and EBV infection that accounts for the similarity in presentation of ICD–10 neurasthenia. In the present study, a sample of Chinese neurasthenia patients was recruited, and their personality, life events, and clinical presentation were subjected to prospective observation and assessment. We also examined serum EBV antibodies. Based on this integrated approach and drawing on key findings from research on CFS, this study aims to extend our knowledgebase regarding the pathogenic factors associated with ICD–10 neurasthenia.

METHOD

Subjects

A group of 30 consecutive patients with neurasthenia were selected from the Mental Health Institute of the Second Xiangya Hospital, affiliated with Central South University in Hunan, China. Although patients with neurasthenia also present in primary-care settings, many patients with neurasthenia are eventually referred to mental health providers after organic explanations for their symptoms are ruled out. Subjects were assessed by a senior and attending physician. Those who fulfilled ICD–10 criteria for neurasthenia in the absence of other mental or physical conditions were recruited into the study. According to the 1:1 paired principle, 30 employees and their relatives or students of Xiangya Hospital matched for sex, age, and education level were randomly selected as control subjects. Individuals with mental and physical disorders were excluded from the control group, as well as those whose score on the Neurotic Screening Scale[21] was ≥ 2. Procedures for this research were approved by the University Research Council of Central South University.

Procedure

Data were collected from May to October 2003. Venous blood was collected from the forearm, and self-report questionnaires were administered to patients and control subjects at baseline and follow-up. Patients were treated with medication as well as psychotherapy. Per standard practice in China, patients received medications that targeted the central nervous system, such as γ-GABA, a stimulator of brain cell metabolism, and γ-oryzanol, as well as benzodiazepines for sleeping problems. Also, patients received a combination of cognitive-behavioral therapy and relaxation training. Because many patients had to travel a significant distance to the hospital, face-to-face therapy sessions were administered on a monthly basis, and weekly consultations were provided over the telephone. Goals of the psychotherapy included symptom relief, medication management, and improvement of coping skills. All participants were all of Han Chinese nationality, and all spoke Chinese as a primary language. We obtained oral and written informed consent for participation in the study.

Measures

Serum EB Virus IgG and IgM Examination Blood was collected once before and after treatment in the neurasthenia group, and once in the control group. Blood sampling was conducted in the afternoon. Serum was obtained, and enzyme-linked-immuno-sorbent assay (ELISA) was used to examine the level of serum EB virus IgG and IgM. All samples were examined in the same batch. The range of variance within batch and between batches ranged from 4.0% to 10.0%.

Symptom Checklist–90 The Chinese version of the Symptom Checklist–90 (SCL–90)[22] was administered as a screening device for measuring symptoms. The SCL–90 is a self-report questionnaire with 90 items rated from 0 to 4 on the basis of the degree of distress caused over the past week. Each item was scored 0: not at all; 1: a little bit; 2:

moderately; 3: quite a bit; or 4: extremely. It includes 10 subscales that assess somatization, obsessive-compulsive traits, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, and additional symptoms and provides a composite score (Global Severity Index [GSI]) as a general indicator of global distress. The SCL–90 was designed for use as a psychiatric case-finding instrument to measure symptom severity and as a descriptive measure of psychopathology.[23] This instrument has been shown to be a reliable and valid psychiatric self-rating scale for use in a variety of populations in China and other countries.[22,23]

The Life Event Scale The Life Event Scale (LES) was used to assess exposure to psychological stress. The LES was developed by Zhang Ya-lin and Yang De-shen;[24] it consists of 48 items. Respondents were presented with positive/negative questions about a variety of life events and were asked to rate the degree of severity of events in the past half-year. Each item was scored 0: not at all; 1: a little bit; 2: moderately; 3: quite a bit; or 4: extremely. The LES provides a total score for life events, a negative-event score, and a positive-event score. The LES has proven useful in general and specific populations. In this study, the test–retest reliability over 2 to 3 weeks[24] was satisfactory ($r = 0.74–0.61$).

The Eysenck Personality Questionnaire The Chinese version of the Eysenck Personality Questionnaire (EPQ–R),[25] edited by Gong Yao-xian, was used to assess the personality of the respondent. It consists of 88 items scored dichotomously as Yes/No. It assesses four factors: Neuroticism, Psychoticism, Extroversion/Introversion, along with a Lie scale. Higher scores on the Extroversion/Introversion factor represent extroversion, whereas lower scores represent introversion. Higher scores on the Neuroticism factor suggest anxiety and worry. Higher scores on the Psychoticism factor suggest solitude and difficulty adapting to the external environment.

Statistical Analysis

SPSS 10.0 statistical software was used for statistical analysis. Paired *t*-tests, chi-square tests, and discriminant-function analysis, as well as correlation analysis were used for comparing the difference between case and control groups, and also within-group comparisons between baseline and follow-up.

RESULTS

In all, 30 patients in the neurasthenia group and 30 control subjects were enrolled in this study. In the neurasthenia group, there were 19 men and 11 women; the mean age was 27.7 years (standard deviation [SD]: 8.4). The duration of illness ranged from 0.6 to 20 years, with an average of 4.0 years. The average education level was 11.7 years (SD: 2.2). Twenty-seven patients were followed during the 4 months of treatment; three patients were lost because of difficulties traveling the long distance to the hospital; all 30 control subjects were retained in the final analysis.

Case–Control Comparisons of Scores for the EPQ and LES and Positive Serum Percentage of EBV

As shown in Table 1, scores for neuroticism (EPQ) and the LES total and negative scores were significantly higher in the neurasthenia group as compared with the controls ($p<0.01$). However, Case scores for extroversion/introversion (EPQ) were lower than those of Controls ($p<0.01$). Among subjects with neurasthenia, the positive rates of serum EB virus IgG and IgM were 76.67% and 26.67%, respectively—significantly higher than the 50.00% for EBV in the Control group ($\chi^2 = 4.59$; $\chi^2 = 7.07$; $p<0.01$).

Self-Report Scores for EPQ, SCL–90, and the Positive Rate of EB Virus Between Baseline and 4-Month Follow-Up

As shown in Table 2, in the neurasthenia group, SCL–90 total scores declined after treatment ($p<0.01$), suggesting that symptoms were improved. Scores for neuroticism (EPQ) were also reduced after treatment ($p<0.01$). The positive rate of EB virus IgG and IgM were 77.78% and 14.81%, respectively, before treatment, similar to the 70.37% and 11.11% after treatment (NS).

Discriminant-Function Analysis of the Possible Pathogenic Factors for Neurasthenia

The occurrence of neurasthenia was considered as the grouping variable, with Psychoticism, Extroversion/Introversion, Neuroticism, Negative Life-Event score, and the level of serum EB virus (IgG and IgM) as predictors.($\alpha = 0.05$). Results indicated that there were two major factors involved in predicting neurasthenia: namely, Neuroticism (X_1) and serum EB virus IgM level (X_2). The discriminant-function equation was F (healthy controls) = $-14.597 + 12.891\ X_1 + 10.460\ X_2$; F (neurasthenia group) = $-26.132 + 0.605\ X_1 + 0.426\ X_2$. A total of 82.1% of Cases were correctly classified.

Correlation of Total Scores for SCL–90 With Total Scores for the LES and Negative-Event Score in the Neurasthenia Group

Scores on the SCL–90 Global Severity Index were positively correlated with total scores for the Life Event scale and Negative-Event score ($r = 0.348$, $r = 0.347$; $p < 0.05$).

DISCUSSION

Although few prospective studies have been conducted to-date, studies suggest that neurasthenia is related to the complex interaction of psychological and social, as well biological, factors.[3,26–28] The present study found that patients in the neurasthenia group had higher scores for neuroticism and endorsed more traits of introversion than the control group. Scores for psychoticism and extroversion/introversion remained stable pre- and posttreatment, whereas scores for neuroticism varied significantly over time. Although these findings are consistent with previous research showing that neuroticism displays the most plasticity in personality,[29] it is also possible that these results are due to the conceptual overlap in assessments of neurasthenia and neuroticism. Specifically, the items used to measure neuroticism may overlap with the symptoms of neurasthenia, so that they may be affected by the symptom and psychological states of subjects over time.

The present study also showed that neurasthenia was strongly related to negative life-events. The total scores for life-events and negative-events scores in the neurasthenia group were significantly higher than those for the control group and positively correlated with psychiatric symptomatology. However, it is unclear whether the onset of neurasthenia is the direct result of life stress, or whether neurasthenia itself creates more life stressors. The definitive causal pathway still requires further study.

In terms of biological factors, research linking EBV infection to chronic fatigue syndrome suggests that EBV may also be associated with the fatigue symptoms prominent in neurasthenia.[15,17,18] Results from the present study provide partial support for this theory. Specifically, the positive rates of serum EBV IgG and IgM in the neurasthenia group were significantly higher than those of the control group. Although not statistically significant, it is also notable that that the improvement of symptoms in patients with neurasthenia after treatment was accompanied by a decreased positive rate of serum EBV. Together, these results provide preliminary evidence that EBV may be associated with neurasthenic symptoms. Moreover, we postulated that internal EBV latency might be what is called a "susceptible property" in neurasthenia. Mental stress has

TABLE 1. Comparison of the EPQ Scores, LES Scores, and Positive Percentage of EBV Between Study and Control Group

	EPQ					LES		EBV	
Group	**P Score**	**E Score**	**N Score**	**L Score**	**Total**	**Positive**	**Negative**	**IgG**	**IgM**
Study group (N = 30)	52.91 ± 14.31	46.31 ± 10.79*	57.59 ± 10.79*	47.08 ± 10.08	19.73 ± 17.25*	0.80 ± 2.34	18.93 ± 17.00*	23* (76.67%)	8 (26.67%)
Control group (N = 30)	49.27 ± 10.58	53.50 ± 11.28	40.58 ± 8.68	45.36 ± 12.00	7.70 ± 10.46	0.47 ± 2.21	7.23 ± 10.24	15 (50%)	0

EPQ: Eysenck Personality Questionnaire; LES: Life Event Scale; EBV: Epstein-Barr virus; P score: Psychoticism; E score: Extraversion/Introversion; L score: Lie scale; IgG: gamma G immunoglobulin; IgM: gamma M immunoglobulin.
*$p < 0.01$ for study (neurasthenia) group as compared with control group.

TABLE 2. Comparison of the EPQ scores, SCL–90 Total Score, and Positive Percentage of EBV Between Baseline and Follow-Up

	EPQ				SCL–90	EBV	
Group	**P Score**	**E Score**	**N Score**	**L Score**	**Total Score**	**IgG**	**IgM**
Baseline (N = 27)	54.36 ± 16.18	44.89 ± 10.14	60.58 ± 9.43*	45.02 ± 10.08	64.55 ± 29.62*	21 (77.78%)	4 (14.81%)
Follow-up (N = 27)	53.72 ± 10.48	46.12 ± 9.73	53.10 ± 12.67	44.89 ± 11.38	50.36 ± 33.43	19 (70.37%)	3(11.11%)

EPQ: Eysenck Personality Questionnaire; P score: Psychoticism; E score: Extraversion/Introversion; L score: Lie scale; SCL–90: Symptom Checklist; EBV: Epstein-Barr virus; IgG: gamma G immunoglobulin; IgM: gamma M immunoglobulin.
*$p < 0.01$ for baseline versus 4-month follow-up.

been found to alter the stability of EBV.[30,31] In one scenario, mental stress up-regulated the expression of hypothalamic corticotropin-releasing hormone, which results in an increment of adrenocorticotrophic hormone that contributes to the release of glucocorticoids by the adrenal cortex. Increased glucocorticoids under stress can stimulate the activation of EBV. Adrenocorticotrophic hormone and adrenocorticotrophic-releasing hormone can also enhance the duplication of EBV.[30,32–34] Although beyond the scope of this study, future research is needed to clarify the potential pathways through which EBV infection may be associated with risk for neurasthenia.

Several limitations of this study are worth noting. The follow-up blood samples and survey data were not collected from the control group as they were in the neurasthenia group. Also, all patients in the neurasthenia group received treatment. Thus, it is unclear whether changes in neuroticism and the positive rate of serum EBV found in the neurasthenia group is the result of treatment effects or normal fluctuations over time. Furthermore, the Life Event Scale, our primary measure of stress due to life-events, was developed and validated on Chinese samples. Although it was an ecologically valid choice for our purposes, we acknowledge that it may be difficult to compare the findings of this study with those of other studies that have used other measures of psychological stress. Despite these shortcomings, the present study suggests that patients with neurasthenia endorse traits associated with neuroticism and introversion, and that they commonly experienced negative life-events before the onset of illness. Moreover, the positive rate of EBV in neurasthenia patients is high, similar to patients with CFS, which may be associated with higher EBV activation under states of stress.

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